REMARKS

In the Office Action of October 31, 2007, the Examiner objected to the specification for including an embedded hyperlink. With the present amendment to the specification, the sentence referring to this government website has now been deleted.

The Examiner has objected to claims 33 and 35 for being dependent on claim 1, which has been canceled.

Claim 33 and 35 have been amended to replace "claim 1" with "claim 21."

Claim 34 and 35 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner has objected to claim 34 for being drawn to a vaccine for combating parasitic infection and claim 35 for being drawn to a method for producing such a vaccine as the present specification fails to provide experiments that show the effectiveness of vaccines for protecting humans or other animals against gram-negative bacterial infection.

With the present amendments, claims 34 and 35 are directed to an immunogenic composition and a method for producing such an immunogenic composition. It is respectfully submitted that the ordinary practitioner would recognize that compositions comprising the attenuated live parasite according to the invention and a pharmaceutically acceptable carrier will raise an immune response when administered to an animal.

Claims 21, 28-32 and 34-35 stand rejected under 35 U.S.C. § 102(b) for being anticipated by Wirtz et al. Claim 21 is drawn to an attenuated live parasite of the phylum Apicomplexa, wherein said parasite comprises a ribosomal protein gene under the control of an inducible promoter. Claim 28 is drawn to an attenuated live parasite wherein the parasite belongs to the genus *Trypanosoma*. Claim 29 is drawn to the attenuated live parasite, wherein said inducible promoter is based on an operator site and a repressor protein capable of reversibly binding said operator site. Claim 30 is drawn to the attenuated live parasite, wherein said inducible promoter is induced by antibiotics. Claim 31 is drawn to the attenuated live parasite, wherein said inducible promoter is inducible by tetracycline. Claim 32 is drawn to the

attenuated live parasite, wherein a tetR-system is used as the inducible promoter. Claim 34 is drawn to a vaccine for combating parasitic infection comprising the attenuated live parasite and a pharmaceutically acceptable carrier. Claim 35 is drawn to a method for production of that vaccine.

The Examiner concluded that Wirtz et al. teaches the inducible expression of transgenes in Trypanosome mediated by the Tet repressor (tetR) inserted in the PARP promoter (page 89), that the promoter was responsive to the antibiotic tetracycline (page 90), conditional gene knockouts while disrupting native alleles thereby providing the attenuated live parasite (page 90), and the generation of transgenic bloodstream-form cell-lines suspended in cytomix, thereby providing for the parasite and a pharmaceutically acceptable carrier (page 93).

The rejection over Wirtz et al. is respectfully traversed. The present invention is based on the discovery that if ribosome synthesis can be stopped at or about the moment of infection, the parasite will enter the host cell and divide using the existing ribosomes. However, after several rounds of dividing the progeny parasites die due to the lack of ribosomes. This goal was achieved by placing a homologous ribosomal protein gene under the control of an inducible promoter, whereby the promoter could be deliberately switched on and off (specification, page 5, lines 27-35).

Applicants claim an attenuated live parasite wherein the parasite comprises a ribosomal protein gene under the control of an inducible promoter.

Wirtz et al. does not regulate the expression of ribosomal proteins. That publication teaches the regulation of the expression of Luciferase and Bleomycin, both of which are non-parasitic proteins (Figure 1, page 91). The locus that Wirtz et al. describes for insertion of an expression cassette is a non-transcribed region of the rRNA gene, which is a region of ribosomal RNA genes and not ribosomal protein genes, as in the present invention. Moreover, Wirtz et al. does not teach the regulation of rRNA genes in the original sequence in the vicinity of the inserted cassette, but the regulation of any gene that may be inserted in their expression cassette. Their construct is not set up to regulate a gene of the parasite in the area of insertion. There is no anticipation of the regulation of a ribosomal protein gene of the parasite.

Claims 21-27 and 29-31 stand rejected under 35 U.S.C. § 103(a) for being obvious over Sutherland et al. in view of Xu et al. Sutherland et al. is relied on for teaching the attenuation of Theileria cell lines for development of live attenuated vaccines, the selection of other avirulent Apicomplexan protozoa resulting in reduced virulence, live attenuated *Babesia* and *Plasmodium* vaccines and the need to control gene expression in such parasites. However, the Examiner acknowledges that Sutherland et al. does not teach that the parasites comprise a ribosomal protein gene under the control of an inducible promoter. Xu et al. is relied on for teaching the expression of genes whose products have a harmful effect and a desire to control gene expression in a wide variety of expression systems, a number of prokaryotic expression vectors that provide controlled gene expression and inducible expression vectors that rely on tightly regulated tetracycline responsive promotors.

The Examiner concluded that it would have been obvious to apply the attenuated live parasites of Sutherland et al. by incorporating a ribosomal protein gene under the control of an inducible promoter as taught by Xu et al. It was concluded that one of ordinary skill in the art would have a reasonable expectation of success by incorporating the ribosomal protein gene under the control of an inducible promoter because Xu et al. teaches that an inducible system advantageously provides stringent regulation of gene expression in prokaryotes, thereby requiring the use of smaller amounts of tetracycline in order to function effectively. Therefore, it would have been prima facie obvious to combine the invention of Sutherland et al. and Xu et al. to advantageously achieve a less toxic, live, attenuated prokaryotic cell line.

The rejection over Sutherland et al. taken with of Xu et al. is respectfully traversed. Sutherland et al. teach no more than the *in vitro* attenuation of Theileria by passaging in culture, resulting in changes in the antibody binding profile. Xu et al. is directed to expression vectors wherein gene expression is controlled by tetracycline regulation. The teaching is directed to introducing regulated functions into cells using viral vectors, particularly directed to cell lines. There is no suggestion of controlling ribosomal protein expression in a parasite with a gene under the control of an inducible promoter.

Claims 21, 28-32 and 34-35 stand rejected under 35 U.S.C. 103(a) for obviousness over Titus et al. taken in view of Yan et al. Titus et al. is said to teach the development of a safe, live, attenuated *Leishmania* vaccine by gene replacement. Titus et al. was said not to teach *Leishmania* comprising a ribosomal protein gene under the control of an inducible promoter. Yan et al. is relied on for teaching tetracycline regulated gene expression in *Leishmania* using an inducible system that provides stringent regulation of gene expression resulting in lower amounts of tetracycline being required to function effectively. Yan et al. is said to teach that the inducer TetR binds to TetO operator and controls transcription from the adjacent promoter and the placement of the promoter in reverse orientation relative to the rDNA transcription locus. The Examiner concluded that it would have been prima facie obvious to apply the attenuated live parasite of Titus et al. and incorporate a ribosomal protein gene under the control of an inducible promoter in order to provide more effective protective *Leishmania* vaccines.

The rejection over Titus et al. taken in view of Yan et al. is respectfully traversed. Titus et al. teach the construction of a DHFR- *Leishmania* mutant by the targeted disruption of an essential gene, crippling the *Leishmania* parasite. This is contrasted with the regulated expression employed by the present invention. Titus et al. do not describe the ribosomal genes as targets for disruption, let alone targets for regulation. Yan et al. also work with *Leishmania*. Following the work of Wirtz et al., Yan et al. replace the T7 promoter with a ribosomal RNA gene promoter to drive expression of a gene of interest. However, they do not regulate a gene at the locus where the expression cassette is inserted, the only gene that is regulated is the gene of interest that has been inserted behind rR and a promoter in a cassette. Again, there is no regulation of a ribosomal protein gene of the parasite as presently claimed. The combination of Titus et al. and Yan et al. would not suggest to the ordinary practitioner to obtain an attenuated live parasite by controlling its ribosomal protein gene using an inducible promoter.

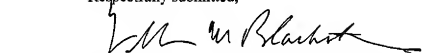
In view of the above it is believed that claims 21-35 are in condition for allowance favorable action is solicited.

Applicants do not believe that any other fee is due in connection with this filing. If, however, Applicants do owe any such fee(s), the Commissioner is hereby authorized to charge

the fee(s) to Deposit Account No. **02-2334**. In addition, if there is ever any other fee deficiency or overpayment under 37 C.F.R. §1.16 or 1.17 in connection with this patent application, the Commissioner is hereby authorized to charge such deficiency or overpayment to Deposit Account No. **02-2334**.

Applicants submit that this application is in condition for allowance, and request that it be allowed. The Examiner is requested to call the Undersigned if any issues arise that can be addressed over the phone to expedite examination of this application.

Respectfully submitted,



William M. Blackstone, PTO Reg. No. 29,772
Chief Patent Counsel
Intellectual Property Department
Intervet Inc., a part of Schering-Plough
P.O. Box 318
29160 Intervet Lane
Millsboro, DE 19966
(302) 934-4317 (tel)
(302) 934-4305 (fax)

WMB:dap